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Research paper

Toxoplasma gondii infection and common mental disorders in the Finnish general population

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ABSTRACT

Objective: We investigated whether *T. gondii* seropositivity is associated with 12-month depressive, anxiety and alcohol use disorders and current depressive symptoms and whether inflammation, measured by C-reactive protein (CRP) level, explains these associations.
Method: Health 2000 study (BRIF8901), conducted in years 2000–2001, is based on a nationally representative sample of Finns aged 30 and above, with 7112 participants and 88.6% response rate. DSM-IV depressive, anxiety and alcohol use disorders were assessed with the Composite International Diagnostic Interview and depressive symptoms with the Beck Depressive Inventory (BDI-21). We used logistic regression to investigate the association of *T. gondii* seropositivity with mental disorders and linear regression with BDI-21 scores.
Results: *T. gondii* seroprevalence was significantly associated with 12-month generalized anxiety disorder but not with other anxiety, depressive or alcohol use disorders. *T. gondii* seropositivity was associated with higher BDI-21 scores (beta 0.56, 95% CI 0.12–1.00, P = 0.013) and with having a comorbid depressive and anxiety disorder (OR 1.86, 95% CI 1.16–2.97, P = 0.010). Higher CRP levels were associated with these outcomes and with *T. gondii* seropositivity, but adjusting for CRP did not change the effect of *T. gondii* seropositivity.
Limitations: Cross-sectional study design with no information on the timing of *T. gondii* infection.
Conclusion: *T. gondii* seropositivity is associated with generalized anxiety disorder, depressive symptoms and comorbid depressive and anxiety disorders, which is not mediated by inflammation.

1. Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular parasite that usually causes an inapparent primary infection but remains then latent in the body and may become reactivated later in life (Saadatnia and Golkar, 2012). The most common sources of infection are ingestion of food or water that is contaminated with oocysts shed by cats or by eating undercooked or raw meat containing tissue cysts (Montoya and Liesenfeld, 2004; Saadatnia and Golkar, 2012).

T. gondii seropositivity has been associated with several mental disorders (Sutterland et al., 2015). A recent meta-analysis investigated its association with schizophrenia, bipolar disorder, major depressive disorder (MDD) and addiction (mainly opioid dependence), and found significant association with schizophrenia, bipolar disorder and addiction but not with MDD (Sutterland et al., 2015). In addition, previous reports have associated *T. gondii* seropositivity with depressive and anxiety symptoms (Groër et al., 2011; Duffy et al., 2015), generalized anxiety disorder (GAD) (Markovitz et al., 2015), obsessive-compulsive disorder (OCD) (Miman et al., 2010), suicidality (Zhang et al., 2012), mixed anxiety and depressive disorder (Alvarado-Esquivel et al., 2016) and aggression and impulsivity (Cook et al., 2015). However, negative findings have also been published (Gale et al., 2014; Sugden et al., 2016).

The prevalence of *T. gondii* seropositivity varies markedly by region, age, and ethnic group (Saadatnia and Golkar, 2012; Sutterland et al., 2015), complicating comparisons between studies. Finland is an ethnically homogeneous Nordic country with relatively low *T. gondii* seroprevalence (von Hertzen et al., 2006). Here, we investigated the association of *T. gondii* seroprevalence and serointensity with mental health in a large, population-based representative sample of adult

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We investigated the association of *T. gondii* seropositivity and serointensity with 12-month DSM-IV anxiety, depressive and alcohol use disorders as well as current depressive symptoms, adjusting for other factors associated with these disorders or with *T. gondii* seroprevalence. Furthermore, we investigated whether the effect of *T. gondii* seropositivity/serointensity could be explained by inflammation, which was measured by sensitive C-reactive protein (CRP) level.

2. Materials and methods

2.1. Participants

The Finnish Health 2000 Survey was based on a nationally representative sample of 8028 persons aged 30 years or over from Finland (Aromaa and Koskinen, 2004). A two-stage stratified cluster sampling design was used to ensure that the sample was representative of the whole country. The sampling frame comprised adults aged 30 years and over living in mainland Finland. The field work took place between September 2000 and June 2001, and consisted of a home interview and a health examination at the local health center, or a condensed interview and health examination of non-respondents at home. In addition, several questionnaires were used to assess symptoms, lifestyle, and exposures related to different health problems. Descriptive data on the participants is presented in Table 1. Plasma samples were collected as a part of the health examination. Stored samples were available from 6250 participants for the current study.

The Health 2000 survey was approved by the Ethical Committee of THL and the Coordinating Ethics Committee at the Hospital District of Helsinki and Uusimaa. Written informed consent was received from each participant.

Table 1
Descriptive information of the participants.

Variable	N with available data on the variable	Proportion (%) or mean with 95% CI
Age	7112	53.0 (52.6–53.4)
Sex:	7112	
Women		52.5% (51.3–53.7%)
Men		47.5% (46.3–48.7%)
Education:	7072	
Basic		40.8% (39.4–42.3%)
Secondary		31.8% (30.7–33.0%)
High		27.3% (26.2–28.5%)
Place of residence:	7112	
Urban		61.4% (55.1–67.6%)
Semi-urban		14.4% (8.4–20.4%)
Rural		24.2% (18.0–30.5%)
Region of residence:	7112	
North		13.4% (13.2–13.8%)
East		17.2% (16.9–17.5%)
West		23.0% (22.5–23.6%)
Southwest		13.5% (13.2–13.8%)
South		32.9% (32.3–33.5%)
Marital status:	7091	
Married or cohabiting		68.0% (66.8–69.2%)
Single, separated or widowed		32.0% (30.8–33.2%)
Cat ownership:	5227	
Current		20.1% (18.7–21.5%)
Previous		54.0% (52.6–55.4%)
Never		25.9% (24.5–27.3%)
12-month depressive disorder	5995	6.5% (5.8–7.2%)
12-month anxiety disorder	6004	4.1% (3.5–4.6%)
12-month alcohol use disorder	5957	4.5% (3.9–5.1%)
Antidepressant use	7112	5.8% (5.3–6.4%)
BDI-21	6311	7.1 (6.9–7.3)
C-reactive protein	6266	2.22 (2.08–2.37)

2.2. Mental health assessment

Mental disorders were assessed using the Munich-Composite International Diagnostic Interview or M-CIDI (Wittchen et al., 1998), using the sections on mood, anxiety and substance use disorders. These sections covered eight DSM-IV diagnoses: MDD and dysthymia, combined as depressive disorders; panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and GAD, combined as anxiety disorders, and alcohol abuse and dependence, combined as alcohol use disorders (Pirkola et al., 2005). The presence of symptoms within the past 12 months (12-month prevalences) were assessed. Of the total sample, 6005 (74.8%) completed the CIDI interview, and blood samples were available for 5917 (98.5%) of them.

In addition, current depressive symptoms were enquired about using the 21-item version of the Beck Depression Inventory (BDI-21) (Beck et al., 1961).

2.3. Sociodemographic variables

We used the following sociodemographic variables in the analysis: age, sex, education and place and region of residence.

Information on general education and on higher and vocational education was combined into a variable describing level of education with three categories. Basic education meant compulsory education with no vocational training beyond a vocational course or on the job training, high meant a degree from higher vocational institutions, polytechnics or universities, and secondary was between these categories, e.g. completion of vocational school. (Aromaa and Koskinen, 2004)

Current place of residence was categorized based on Statistics Finland's classification as urban, semi-urban and rural. Region of residence was categorized based on the university hospital districts as Northern, Eastern, Western, Southwestern, and Southern Finland.

2.4. Other variables

The participants were asked about cat ownership in a questionnaire, categorized as current, previous and never. This variable was added in the models, because domestic cats are a potential source of infection.

A previous Nordic study has found that *T. gondii* seropositivity is associated with higher values of C-reactive protein (CRP) (Birgisdóttir et al., 2006), which in turn is associated with both depression (Young et al., 2014) and anxiety (Copeland et al., 2012). Therefore, we investigated whether associations between mental health and *T. gondii* seropositivity changed after adjusting for CRP level. Serum high-sensitivity CRP levels (mg/L) had been measured in the Health 2000 study using automated analyser (Optima, Thermo Electron Oy, Vantaa, Finland) and an immunoturbidimetric test (Ultrasensitive CRP, Orion Diagnostica, Espoo, Finland), as described in detail in Heikkilä et al. (2011).

We controlled for the effect of antidepressant use, because one previous study found suggestive evidence that they may be associated with serointensity in patients with MDD (Hinze-Selch et al., 2007).

2.5. T. gondii IgG level measurement

Concentration of IgG antibodies to Toxoplasma gondii was measured by solid phase enzyme immunoassay employing whole tachyzoite lysate from Ross South Labs, Spanish Fork Utah, USA employing methods similar to those which have been previously described (Dickerson et al., 2007). Sample values were converted to international units by comparison to standards with known levels of antibody.

We used 50 IU/ml as the cut-off for seropositivity, as in Sugden et al. (2016). In addition, serointensity, defined as the quantitative level of

antibody in IU/ml, was analyzed as a continuous variable.

2.6. Statistical analysis

Statistical analyses were conducted using the SUDAAN software, Release 11.0.1, which takes the two-stage cluster sampling design into account. In addition, post-stratification weights calibrated in Statistics Finland were applied to adjust for non-response and for the over-sampling of individuals aged 80 years and over.

We calculated the prevalence of toxoplasma seropositivity by sociodemographic features, cat ownership and mental disorders, adjusting for age and sex. This was done using SUDAAN's RLOGIST procedure, calculating predictive margins using the PREDMARG command. These predictive margins were adjusted for age and sex and provide more comparable results than the crude prevalences (Bieler et al., 2010). Similar analysis for serointensity was performed using SUDAAN's REGRESS procedure.

We used logistic regression (SUDAAN's RLOGIST) to investigate the association of *T. gondii* seropositivity with mental disorders, after adjusting for other variables associated with mental disorders or *T. gondii* seroprevalence. Besides investigating the association of *T. gondii* seropositivity with 12-month depressive, anxiety and alcohol use disorders separately, we also investigated whether it was associated with comorbid depressive and anxiety disorders. Linear regression (SUDAAN's REGRESS procedure) was used to investigate the association of *T. gondii* seropositivity with current depressive symptoms after adjusting similarly for other relevant variables. In regression models including CRP levels, also the interaction between *T. gondii* seropositivity and CRP level was tested. All statistical tests were two-tailed, and $p < .05$ was used to define a significant difference.

3. Results

3.1. Toxoplasma seroprevalence and its association with sociodemographic factors

The seroprevalence of *T. gondii* in the study population was 19.7% (95% CI 18.3–21.2%) (Supplementary Table 1). Seroprevalences in men and women in different age groups are reported in Supplementary Table 2. The seroprevalence of *T. gondii* was highest in the southwestern and lowest in the northern Finland, with no significant urban-rural differences. Seroprevalence was higher in women than in men and increased by age, with no significant differences by education or marital status. People who currently had a cat had a higher seroprevalence rate than those who had previously or never had a cat. (Supplementary Table 1)

3.2. Toxoplasma seroprevalence and mental health

Adjusting for age and sex, *T. gondii* seroprevalence was not higher in people with 12-month anxiety, depressive or alcohol use disorders, although there was a suggestive association between seroprevalence and anxiety disorders (P = 0.08) (Table 2). We further analyzed different anxiety and depressive disorders separately. With the exception of agoraphobia, the prevalence was higher in all diagnostic groups in those who were *T. gondii* seropositive than in *T. gondii* seronegative, but this was statistically significant only for GAD (Table 2). Separate analyses for men and women are reported in Tables 3 and 4 and revealed a significantly higher prevalence of dysthymia in *T. gondii* seropositive men and a significantly higher prevalence of GAD in *T. gondii* seropositive women than in those who were seronegative.

People who were *T. gondii* seropositive had higher BDI-21 scores: the age- and sex-adjusted mean score was 7.5 (95% CI 7.0–7.9) in those who were seropositive and 6.9 (95% CI 6.7–7.1) in those who were seronegative (P = 0.009). When this was analyzed separately for men and women, women who were *T. gondii* seropositive had significantly higher BDI scores (8.6 (95% CI 8.0–9.1)) than women who were seronegative (7.6 (95% CI 7.3–7.9), P = 0.001), but in men there were no significant differences between the groups (mean BDI in seropositives

Table 2
12-month prevalence of different anxiety and depressive disorders in participants who were toxoplasma seropositive or seronegative; calculated as predictive margins adjusting for age and sex.

Psychiatric disorder	Prevalence in *T. gondii* seropositive (% with 95% CI)[a]	Prevalence in *T. gondii* seronegative (% with 95% CI)[a]	P-value (Wald χ^2)
Panic disorder	2.4% (1.7–3.6%)	1.8% (1.4–2.3%)	0.17
Agoraphobia	0.5% (0.2–1.1%)	0.6% (0.4–0.8%)	0.88
GAD	1.9% (1.2–3.0%)	1.2% (0.9–1.5%)	**0.04**
Social phobia	1.5% (0.9–2.6%)	0.9% (0.7–1.2%)	0.09
Any anxiety disorder	5.1% (3.8–6.6%)	3.8% (3.3–4.5%)	0.08
MDD	5.0% (3.8–6.6%)	4.8% (4.2–5.4%)	0.75
Dysthymia	2.8% (2.0–3.9%)	2.3% (1.9–2.8%)	0.33
Any depressive disorder	6.8% (5.4–8.6%)	6.3% (5.6–7.1%)	0.53
Both anxiety and depressive disorder	2.5% (1.7–3.8%)	1.4% (1.1–1.7%)	**0.01**
Alcohol use disorder	4.3% (3.1–6.0%)	4.5% (4.0–5.2%)	0.76

[a] Adjusted for age and sex.

Table 3
12-month prevalence of different anxiety and depressive disorders in men who were toxoplasma seropositive or seronegative; calculated as predictive margins adjusting for age.

Psychiatric disorder	Prevalence in *T. gondii* seropositive (% with 95% CI)[a]	Prevalence in *T. gondii* seronegative (% with 95% CI)[a]	P-value (Wald χ^2)
Panic disorder	2.1% (1.0–4.2%)	1.3% (0.8–1.9%)	0.24
Agoraphobia	0.7% (0.2–2.1%)	0.5% (0.3–0.9%)	0.68
GAD	1.5% (0.7–3.2%)	1.2% (0.8–1.9%)	0.72
Social phobia	1.9% (0.9–2.9%)	1.0% (0.7–1.5%)	0.13
Any anxiety disorder	4.3% (2.7–6.7%)	3.4% (2.7–4.2%)	0.39
MDD	3.8% (2.3–6.0%)	3.3% (2.6–4.2%)	0.64
Dysthymia	3.2% (1.9–5.3%)	1.6% (1.1–2.3%)	**0.032**
Any depressive disorder	5.6% (3.7–8.2%)	4.3% (3.5–5.3%)	0.28
Alcohol use disorder	6.8% (4.7–9.7%)	7.9% (6.8–9.1%)	0.44

[a] Adjusted for age.

Table 4
12-month prevalence of different anxiety and depressive disorders in women who were toxoplasma seropositive or seronegative; calculated as predictive margins adjusting for age.

Psychiatric disorder	Prevalence in *T. gondii* seropositive (% with 95% CI)[a]	Prevalence in *T. gondii* seronegative (% with 95% CI)[a]	P-value (Wald χ^2)
Panic disorder	2.8% (1.8–4.4%)	2.3% (1.7–3.0%)	0.41
Agoraphobia	0.4% (0.1–1.2%)	0.6% (0.3–1.0%)	0.57
GAD	2.2% (1.4–3.6%)	1.1% (0.7–1.5%)	**0.016**
Social phobia	1.3% (0.6–2.6%)	0.9% (0.6–1.3%)	0.42
Any anxiety disorder	5.7% (4.1–7.9%)	4.2% (3.5–5.2%)	0.14
MDD	6.3% (4.6–8.6%)	6.2% (5.3–7.2%)	0.91
Dysthymia	2.8% (1.8–4.2%)	3.0% (2.4–3.8%)	0.71
Any depressive disorder	8.2% (6.3–10.6%)	8.2% (7.1–9.4%)	0.98
Alcohol use disorder	1.9% (1.0–3.6%)	1.4% (1.0–2.0%)	0.42

[a] Adjusted for age.

6.2 (95% CI 5.6–6.8) and in seronegatives 6.1 (95% CI 5.8–6.4), P = 0.73). Using the ≥ 14 cut-off for at least mild depressive symptoms, 17.5% (95% CI 15.3–20.0%) of *T. gondii* seropositive participants had at least mild current depressive symptoms, compared to 14.5% (95% CI 13.5–15.5%) of *T. gondii* seronegative participants (P = 0.014). Of note, people with 12-month anxiety disorder had similar BDI-21 scores as those with 12-month depressive disorder: adjusting for age and sex, the mean BDI-21 score was 17.4 (95% CI 16.1–18.8) in those with 12-month anxiety disorder and 17.1 (95% CI 16.1–18.1) in those with 12-month depressive disorder.

We investigated whether *T. gondii* seropositivity was a significant predictor of 12-month anxiety or depressive disorders after adjusting for factors known to increase the prevalence of anxiety disorders or *T. gondii* seroprevalence: age, sex, region of residence, education, marital status, cat ownership and other 12-month diagnoses. *T. gondii* seropositivity was not a significant predictor in these logistic regression models. Analogously, we investigated whether *T. gondii* seropositivity was a significant predictor of BDI scores, adjusting for age, sex, region of residence, education, marital status, cat ownership and 12-month diagnoses. *T. gondii* seropositivity remained significantly associated with higher BDI scores (beta 0.56, 95% CI 0.12–1.00, P = 0.013).

3.3. Effect of inflammation

Adjusted for age and sex, *T. gondii* seropositivity was associated with higher CRP levels (2.6, 95% CI 2.2–2.9 vs. 2.1, 95% CI 2.0–2.3, P = 0.045). When CRP was added to the regression models, the results regarding *T. gondii* seropositivity did not change. CRP was a significant predictor of 12-month anxiety disorders (OR 1.02, 95% CI 1.01–1.03, P = 0.002) but not 12-month depressive disorders. *T. gondii* seropositivity remained a significant predictor of BDI score (beta 0.55, 95% CI 0.11–0.99, P = 0.014) after adjusting for CRP, whereas CRP was a significant predictor of higher BDI scores as well (beta 0.047, 95% CI 0.02–0.07, P < .001). Results from this model are presented in Table 5.

3.4. Effect of current antidepressive use

As a sensitivity analysis, we investigated whether adjusting for current antidepressive use changes the results. Antidepressive use was not significantly associated with seropositivity (Supplementary Table 1), and adjusting for it did not change the non-significant findings related to 12-month disorders or the significant association of *T. gondii* seropositivity with current depressive symptoms (P = 0.018).

3.5. Effect of having concurrent anxiety and depressive disorder

Of those with 12-month depressive disorder (n = 391), 24.6% (n = 96) also had an anxiety disorder, whereas 39.8% (n = 96) of those with 12-month anxiety disorder (n = 241) also had a depressive disorder. All depressive and anxiety disorders were associated with higher seroprevalence rates, although the effect was not significant for any individual disorder. Based on this and the significant association between current depressive symptoms, we investigated whether *T. gondii* seropositivity was associated with comorbid anxiety and depressive disorder. We found that the prevalence of a comorbid depressive and anxiety disorder was significantly higher (2.5%, 95% CI 1.7–3.8%) in those who were *T. gondii* seropositive than in those who were seronegative for *T. gondii* (1.4%, 95% CI 1.1–1.7%) (Table 2). Adjusting for age, sex, region of residence, education, marital status and cat ownership, *T. gondii* seropositivity was significantly associated with having comorbid depressive and anxiety disorder (OR 1.73, 95% CI 1.02–2.92, P = 0.042). Further adjustment for CRP did not affect the association of comorbid depressive and anxiety disorder with *T. gondii* seropositivity (OR 1.72, 95% CI 1.02–2.91, P = 0.043), while the effect of CRP was also significant (OR 1.02, 95% CI 1.00–1.04, P = 0.015).

3.6. Toxoplasma serointensity

When the quantitative level of antibody was investigated instead of dichotomous seropositivity, *T. gondii* serointensity remained a significant predictor of BDI score (P = 0.017) after adjusting for age, sex, region, education, cat ownership and 12-month mental disorders, and remained significant (P = 0.019) also after CRP and antidepressive use were added in the model. In contrast, the association of serointensity with GAD or comorbid anxiety and depressive disorder did not reach statistical significance in the full model. When this analysis was restricted to *T.gondii* seropositive participants only, *T. gondii* serointensity and CRP level both lost their statistical significance.

4. Discussion

Consistent with previous studies (Groër et al., 2011; Duffy et al., 2015), *T. gondii* seropositivity and serointensity were associated with current depressive symptoms. They were not associated with 12-month depressive disorders with the exception of dysthymia in men. Lack of association with MDD is consistent with the meta-analysis by Sutterland et al. (2015) and with findings from the National Health and Nutrition Survey (Pearce et al., 2012), although high serointensity has previously been associated with MDD (Hinze-Selch et al., 2007). We found a significant association between *T. gondii* seropositivity and GAD, which is consistent with the study by Markovitz et al. (2015) but not with the NHANES study (Gale et al., 2014). Furthermore, *T. gondii* seropositivity predicted having both depressive and anxiety disorder concurrently. The finding concerning comorbidity between depressive and anxiety disorders is consistent with the recent study on mixed anxiety and depressive disorders (9).

Although the association between *T. gondii* seropositivity and anxiety disorders was statistically significant only for GAD, the finding was fairly similar for social phobia and panic disorder as well, suggesting that *T. gondii* seropositivity is associated with anxiety. Unfortunately, the Health 2000 Survey did not include a specific measure of anxiety symptoms. However, the significant association with current depressive symptoms and comorbid depressive and anxiety disorder also implies that *T. gondii* seropositivity and serointensity are associated with more severe forms of depression and anxiety. This would fit with previous associations of *T. gondii* seropositivity with suicide attempts (Pedersen et al., 2012; Alvarado-Esquivel et al., 2013).

Table 5
Linear regression model of Beck Depression Inventory (BDI-21) score; adjusted for age, sex, education, region of residence, marital status and cat ownership.

Variable[a]	Beta coefficient (95% confidence interval)	Wald χ^2 (degrees of freedom in parentheses)	P value
Toxoplasma seropositive	0.55 (0.11–0.99)	6.00 (1)	0.014
12-month alcohol use disorder	3.65 (2.49–4.81)	37.9 (1)	< .001
12-month depressive disorder	9.10 (8.04–10.11)	287.9 (1)	< .001
12-month anxiety disorder	6.06 (4.77–7.35)	85.0 (1)	< .001
CRP (mg/l)	0.047 (0.02–0.07)	12.3 (1)	0.001

[a] All variables (age, sex, education, region of residence, marital status, cat ownership, toxoplasma seropositivity, 12-month disorders and CRP) were entered simultaneously in the model.

Unfortunately, data on suicidal ideation and attempts were not systematically collected in the current study. Higher IgG levels may be related to higher rate of exposure to *T. gondii* in people with current depressive symptoms, but could also reflect a more recent infection, or reactivation of a latent infection (Montoya, 2002).

Two previous studies have reported that *T. gondii* seropositivity is associated with higher CRP level (Birgisdóttir et al., 2006; Hinze-Selch et al., 2007), which has also been observed in a mouse model of chronic *T. gondii* infection (Tomasik et al., 2016). Elevated CRP, in turn, may predispose to depressive symptoms (Valkanova et al., 2013). Consistently with previous research, CRP was associated both with *T. gondii* seropositivity and with depressive symptoms and 12-month anxiety disorders. However, adjusting for CRP level did not change the significant association between *T. gondii* seropositivity and current depressive symptoms, suggesting that the effect of *T. gondii* was not mediated by inflammation. A recent study found an association between unipolar depression and cat scratches, but not with *T. gondii* seropositivity, suggesting that another pathogen than *T. gondii*, possibly the agent causing cat-scratch disease might explain the association (Flegr and Hodný, 2016). In our analyses, we controlled for cat ownership but did not have information on cat scratches.

The seroprevalence of *T. gondii* in our study of individuals in Finland was 19.7%. Globally, *T. gondii* seroprevalence is highest in warm and humid climates and in populations with low socioeconomic status, whereas seroprevalence rates found in Iceland and Norway, other Nordic countries with long, snowy winters, are similar to our finding (Pappas et al., 2009). The prevalence in eastern Finland, 18.0%, is slightly higher than in a previous study which found 7.0% seropositivity for *T. gondii* in eastern Finland using the complement fixation test (von Hertzen et al., 2006). In this study, the seroprevalence was almost three times higher in geographically adjacent Russian Karelia, showing the importance of environmental factors in addition to climate on seroprevalence rates (von Hertzen et al., 2006). Consistently with previous research, current cat ownership was a risk factor for *T. gondii* seropositivity. About half of domestic cats in Finland are seropositive for *T. gondii*, with no geographic variation in seroprevalence rates (Jokelainen et al., 2012). Undercooked meat could be another route of exposure; *T. gondii* has been found from moose, deer and domestic sheep in Finland, with a clear geographical gradient in these animals (Jokelainen et al., 2010).

The major strength of the study is that due to its sampling design, the Health 2000 study sample is representative of the adult Finnish population (Aromaa and Koskinen, 2004), and the participation rate was excellent: 88.6% to the health interview or examination and 74.8% to the CIDI interview. Sampling weights were used to adjust for sampling variability and non-response. Therefore, the findings can be generalized to the whole adult Finnish population.

5. Limitations

Despite having a large population-based study sample, the number of participants with anxiety and depressive disorders was still limited, and the lack of significant association of *T. gondii* with several anxiety disorders despite higher point prevalence in seropositivity and higher serointensity may reflect limited statistical power. Statistical power in detecting significant differences in a continuous variable like BDI was better. We did not use any correction for multiple comparisons. Finland is a Nordic country with low *T. gondii* seroprevalence compared to most other countries. The meta-analysis by Sutterland et al. (2015) found a stronger association between *T. gondii* and mental disorders in Africa, South America, Asia and the Middle East than in Europe or North America, which could indicate strain-specific effects. Therefore, it is possible that the reported associations would be stronger in countries with higher seroprevalence rates. In addition, timing of the infection was not known in the current study. This would be important in order to understand whether the observed associations between *T. gondii* seropositivity and depressive symptoms, GAD and comorbid anxiety and depressive disorders were caused by a recent infection or by a reactivation of a latent infection.

6. Conclusions

This study adds to the previous literature on the impact of *T. gondii* infection on mental health. We found that people who were *T. gondii* seropositive had more depressive symptoms, and *T. gondii* seropositivity was also associated with comorbid depressive and anxiety disorders and with GAD. While the most apparent contribution on the total disease burden attributed to *T. gondii* globally arises from congenital toxoplasmosis and toxoplasmosis in immunocompromised host (Opsteegh et al., 2015), there is growing evidence of its significance as a risk factor for several mental disorders (Sutterland et al., 2015) as well as aggression and impulsivity (Cook et al., 2015; Coccaro et al., 2016) and other health problems (Flegr and Escudero, 2016).

According to a European multicentre case-control study in pregnant women, the main sources of infection in European populations were inadequately cooked or cured meat, contact with soil, working with animals and travel outside Europe or United States and Canada (Cook et al., 2000). Drinking unpasteurised milk or untreated water was also important in some countries (Cook et al., 2000). Until an effective *T. gondii* vaccine for cats is developed and implemented, prevention of *T. gondii* infections needs to focus on reducing exposure to food-borne infections and infections arising from contact to contaminated soil or water through health education and decontamination of meat products (Opsteegh et al., 2015). Since cats become infected mainly through hunting and eating infected animals, keeping them indoors will lower the rate of infection, and also prevents oocysts from infected cats ending up in the environment (Opsteegh et al., 2015).

Consistent with previous studies, *T. gondii* seroprevalence and serointensity were associated with current depressive symptoms but not with 12-month depressive disorders. These findings raise questions: is this related to having a recent infection? Or is it possible that current depressive symptoms trigger reactivation of a latent infection, reflected as a higher antibody level? Yet another possibility is that *T. gondii* infection is associated with more severe and persisting depressive symptoms. Longitudinal studies on patients with depressive and anxiety disorders are needed to further evaluate the role of *T. gondii* infection in these disorders.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.07.020.

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